SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 4-FUNCTIONAL PYRAZOLES AND THEIR DERIVATIVES

SYNOPSIS

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For the degree of

DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

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SYNOPSIS

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1. **Title:** SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 4-FUNCTIONAL PYRAZOLES AND THEIR DERIVATIVES

2. Introduction

Amongst heterocycles, pyrazole derivatives occupy a central place in our armamentarium against various diseases afflicting mankind because of their diverse biological activities such as herbicidal, fungicidal, insecticidal, analgesic, antipyretic and anti-inflammatory properties (Elguero 1984; Elguero 1986). It is considered a typical model of pyrazole containing, diaryl-heterocyclic template that is known to selectively inhibit (cyclooxygenase enzyme) cox-2 (Palomeret al 2002). Celecoxib is shown to be potent and gastrointestinal (GI) safe anti-inflammatory and analgesic agent. Much attention is given to pyrazoles as antimicrobial agents after the discovery of the natural pyrazole C-glycoside, pyrazofurin which demonstrated a broad spectrum of antimicrobial activity (Kucukguzel et al 2000; Genin et al 2000). Recently, 4-functionally substituted 1,3-diaryl pyrazole derivatives have received considerable attention due to their multiple biological properties (Thumar and Patel 2009). 4-Formyl pyrazoles attracted special attention in medicinal chemistry since these constitutes the core scaffold of several biologically active synthetic heterocyclic compounds having interesting pharmaceutical properties (Khloya et al 2013). In the series of functionally substituted pyrazoles, 4-pyrazole carboxylic acids are very important. On their capability to decarboxylate at elevated temperature is based on extensively used preparation method for pyrazoles unsubstituted in 4-postion (Bratenko et al 2001). Beside some derivatives of 4-pyrazole carboxylic acids, e.g. amides, possess pronounced pharmaceutical activity (Bratenko et al 2001). The oxidation of 4-pyrazole carbaldehyde is a promising approach in the synthesis of the pyrazole-substituted carboxylic acids.

On the other hand, benzothiazole possess various biological and pharmacological properties, and its derivatives have led to multiple uses of these compounds as important intermediates in organic synthesis (Bhoi et al 2014). Benzothiazole derivatives are used as important components such as local anesthetics (Costakes and Tsabsas 1979), hypoglycemic agents (Chernykh and Sidorenko 1983), carbonic anhydrase inhibitors (Wollesdrof and Schwam 1989), enzyme inhibitors (Greco et al 1992), choleratic agent (Strelets et al 1985), central dopaminergic agents (Millard 1985), industrial applications such as antioxidants

(Duangkaewmanee and Petsom 2011; De Brabander et al 1999), vulcanization accelerators (Morgan and McGill 2000), electroluminescent devices (Zhang et al 2001) and in pharmaceuticals such as in the diabetic drug, zopolrestat (Mylari et al 1991), and the fatty acid oxidation inhibitor CVT-3501 (Koltun et al 2004).

Based on the remarkable pharmacological efficiency of pyrazole and benzothiazole, derivatives and the idea that the incorporation of both pyrazole and benzothiazole together in the same scaffold could provide novel compounds with interesting biological activities, we thought worthwhile to synthesize 4-functionalized pyrazole derivatives.

The main objectives of the present research work are depicted below:

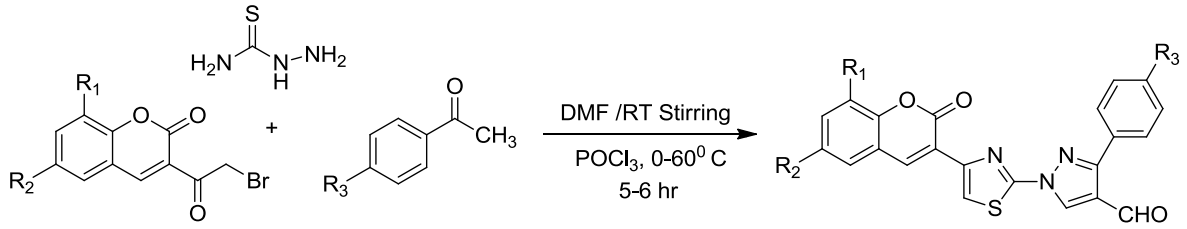
a) Development of synthetic routes and purification methods for the newly synthesized compounds.
b) Synthesis of 4-functionally substituted 1-benzothiazolylpyrazoles which are precursors for many nitrogen & sulphur containing heterocyclic compounds.
c) Characterization of new compounds by IR, ^{1}H NMR, Mass spectral studies and also by elemental analysis.
d) Evaluation of biological activities of new compounds, such as antimicrobial activity using different bacterial and fungal strains.
e) Study of structure activity relationship with reference to biological activity.

3. Expected new knowledge

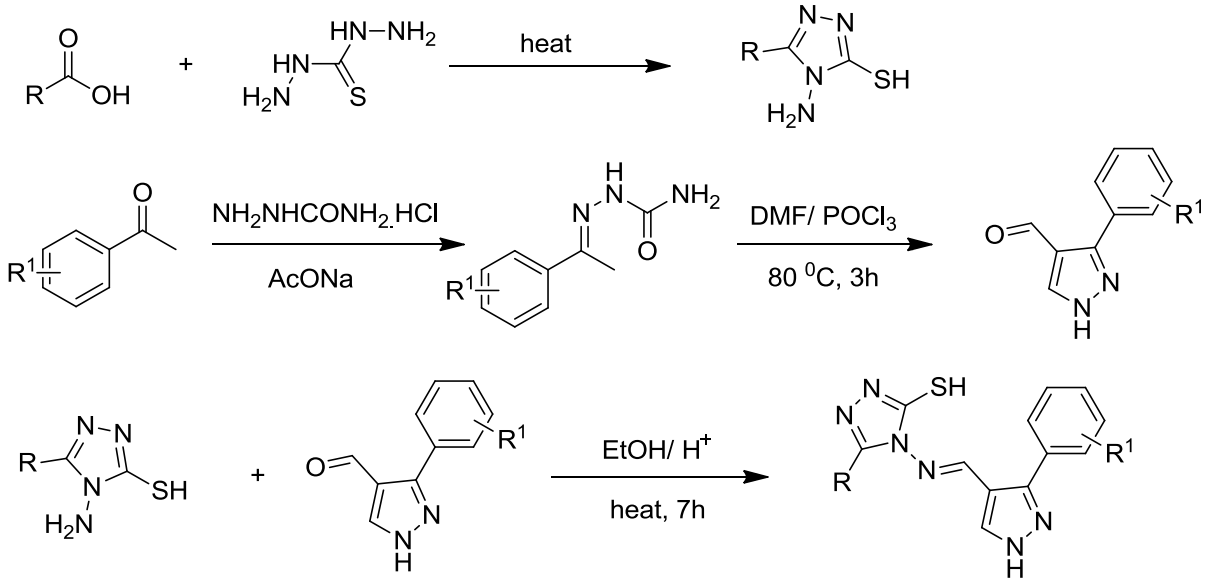
As a result of remarkable pharmacological efficiency of pyrazole and benzothiazole, derivatives, our studies are focused towards the synthesis, characterization and biological evaluation of various 4-functionally substituted 1-benzothiazolylpyrazoles. Infectious diseases have emerged as a serious cause of morbidity and mortality worldwide. The diseases like pneumonia, tuberculosis (TB), typhoid, influenza, dengue and HIV are matter of big concern at present. Further, antimicrobial resistance is a global public health concern that impacted by both human and non-human antimicrobial use. The greatest impact of the synthesis of heterocyclic chemistry is the development of new pharmaceutically active and efficient compounds. Heterocyclic compounds by virtue of their specific activity could be employed in the treatment of infectious diseases. Research studies have indicated the remarkable pharmacological efficiency of pyrazole and benzothiazole derivatives. This gives us an opportunity to explore new molecules. Therefore, our studies are focused towards the synthesis of 4-functionally substituted 1-benzothiazolylpyrazoles by hybrid approach and used them for the biological evaluation. It is expected that the study of structure-activity relationship (SAR) of the new compounds will impart structural elements for new drug designing and synthesis of these compounds will impart a great role to extend the method to a broad range of different starting materials to find the scope and limitations.

4. Review of literature

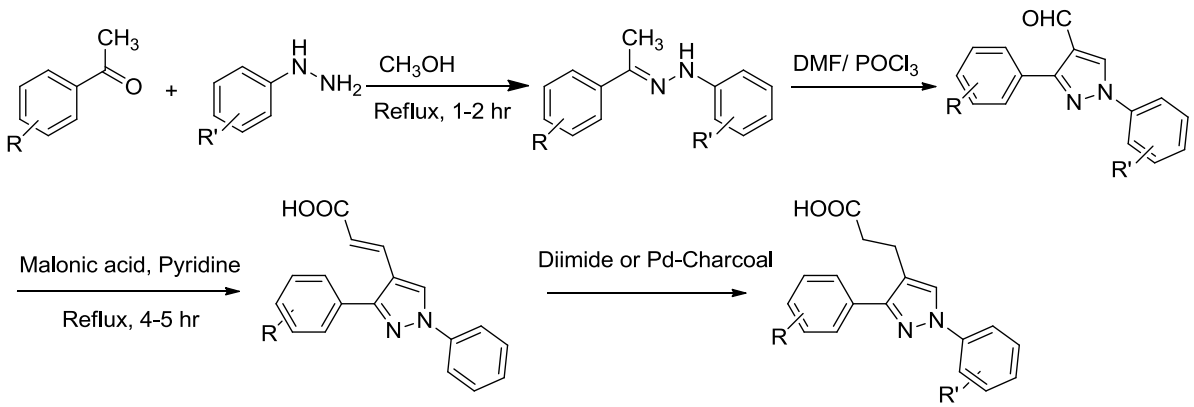
Vaarla and co-workers (2015) reported an efficient, one-pot multi component approach for the synthesis of coumarin substituted thiazolyl-3-arylpyrazole-4-carbaldehydes. Treatment of 3-(2-bromoacetyl)coumarins, thiosemicarbazide and substituted acetophenones with Vilsmeier-Haack reagent resulted the target compounds with good yields.



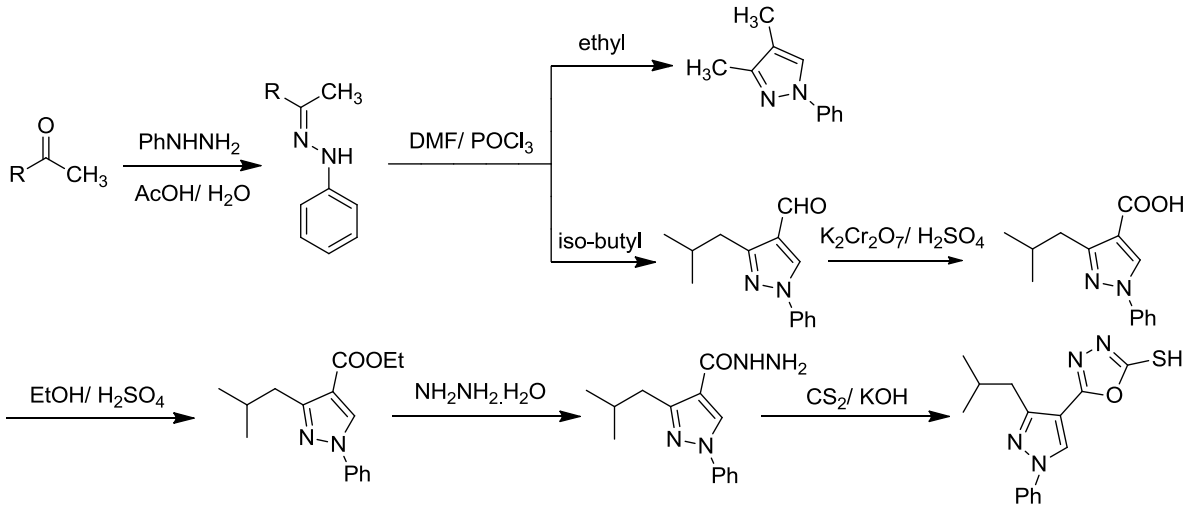
Malladi et al (2013) reported the synthesis of Schiff bases which were prepared by the condensation of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol with several 3-substituted-pyrazole-4-carboxaldehydes in the presence of concentrated sulfuric acid in ethanol-dioxane mixture.



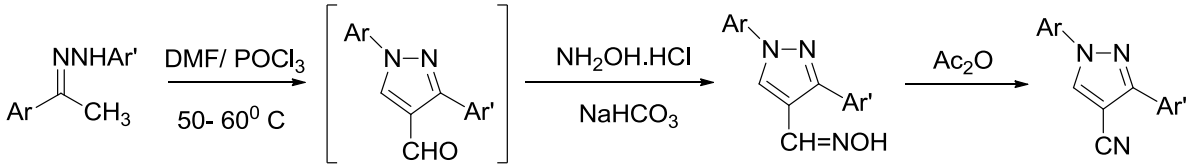
Pyrazole-1*H*-4-yl-acrylic acids were synthesized from pyrazole-1*H*-4-carbaldehydes which in turn were prepared by the Vilsmeier-Haack reaction of phenyl hydrazone derivatives. The conversion of pyrazole-1*H*-4-yl-acrylic acids to 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)propanoic acids was carried out using Pd-charcoal and diimide methods and % yields were compared. Though the yields may be slightly less in diimide method, the method was found to be economical, highly effective with simple operating procedure (Deepa et al 2012).



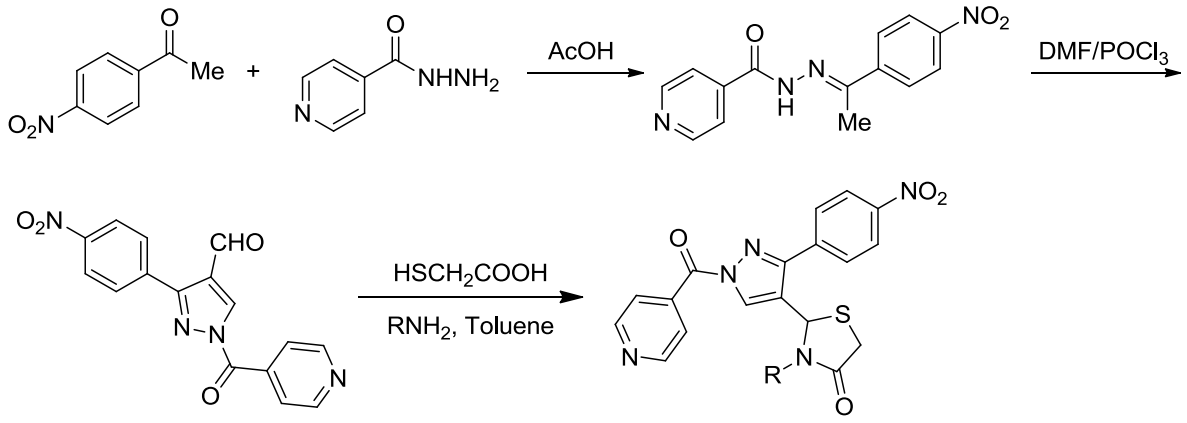
Abu-Zaied et al (2011) reported the formation of 3-isobutyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde *via* condensation between methyl iso-butyl ketone and phenylhydrazine followed by application of Vilsmeiere Haack reaction. 3-isobutyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde was converted to 1,3,4-oxadiazole derivative.



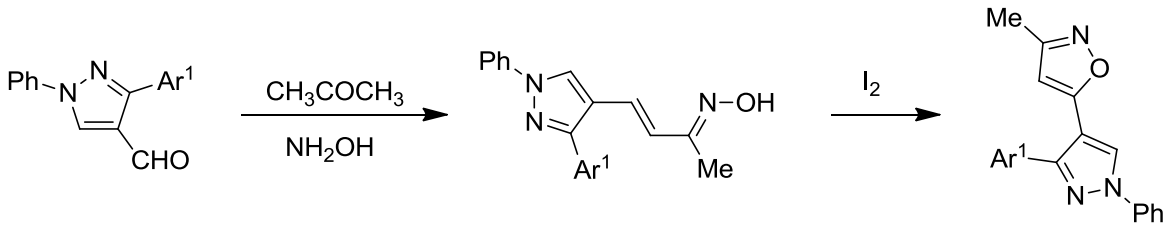
Prakash et al (2009) reported a mild, short and simple method for the small scale synthesis of pharmaceutical important 1,3-diaryl-4-cyanopyrazoles.



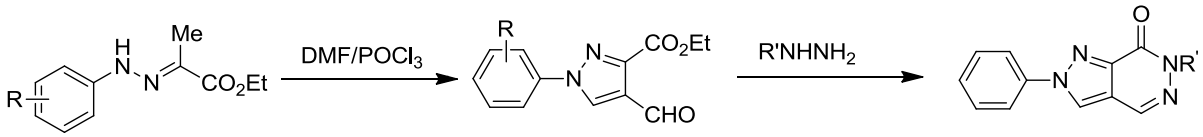
Visagaperumal et al (2009) reported the synthesis of pyrazolylthiazolidin-4-one by the reaction of 3-(4-nitrophenyl)-1-(pyridin-4-ylcarbonyl)-1*H*-pyrazole-4-carbaldehyde with 2-mercaptoacetic acid and several substituted aromatic amines in toluene. 3-(4-nitrophenyl)-1-(pyridin-4-ylcarbonyl)-1*H*-pyrazole-4-carbaldehyde was prepared by using Vilsmeier Haack reagent from *N'*-[1-(4-nitrophenyl)ethylidene]benzohydrazide which was synthesized from reaction of 4-nitroacetophenone and hydrazide**,** in the presence of acetic acid.



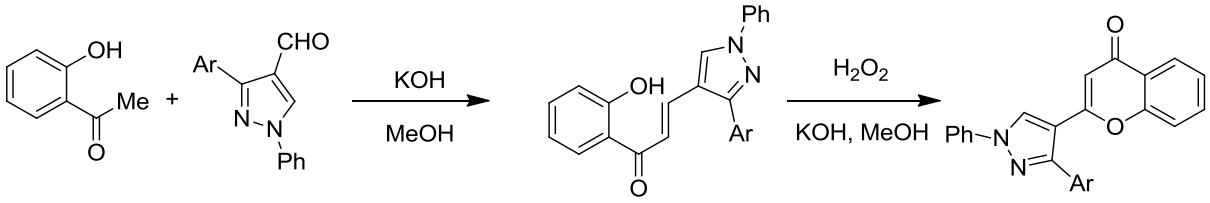
Oximes of 4-(4-pyrazolyl)-3-buten-2-ones**,** obtained by successive reaction of 4-formylprrazoles with acetone and hydroxylamine, upon treatment with iodine suffered an oxidative cyclization, yielding 4-(5-isoxazolyl)pyrazoles [Bratenko et al 2008].



Matiichuk et al (2008) reported the synthesis of 2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-ones. The several ethyl 2-(arylhydrazono)propanoates were reacted with the Vilsmeier-Haack reagent to give ethyl 1-aryl-4-formyl-1*H*-pyrazole-3-carboxylates**.** Reactions of pyrazole derivatives with hydrazine and methylhydrazine led to the formation of the corresponding 2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-ones.

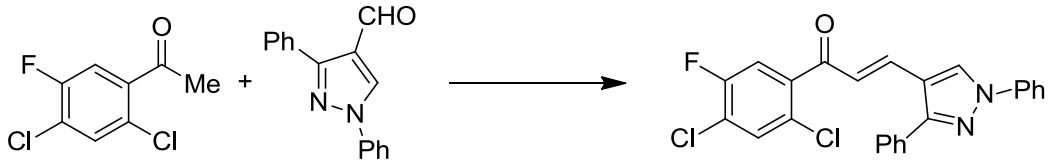


Pyrazole-4-carbaldehyde was reacted with 2-hydroxyacetophenone in methanol in the presence of KOH to give chalcone which on oxidation with hydrogen peroxide in KOH/MeOH afforded 2-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-chromen-4-ones in high yields (Prakash et al 2008).

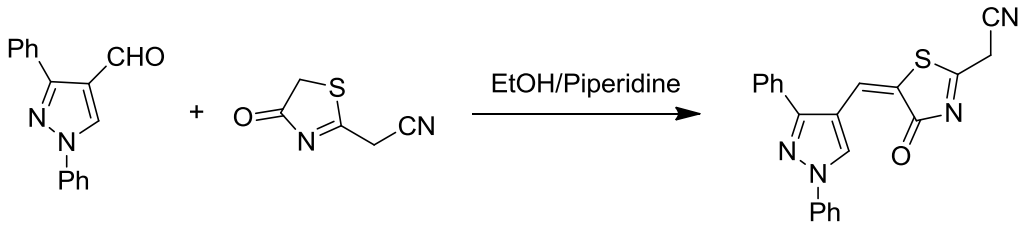


2,4-Dichloro-5-fluoroacetophenone was reacted with 1,3-diphenyl-1*H*-pyrazole-4-

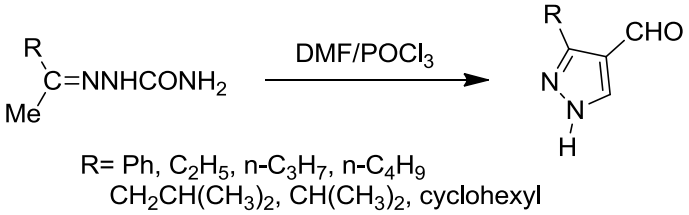
carbaldehyde to give 1-(2,4-dichloro-5-fluorophenyl)-3-(1,3-diphenyl-1*H*-pyrazole-4-yl) prop-2-en-1-one [More et al 2006].



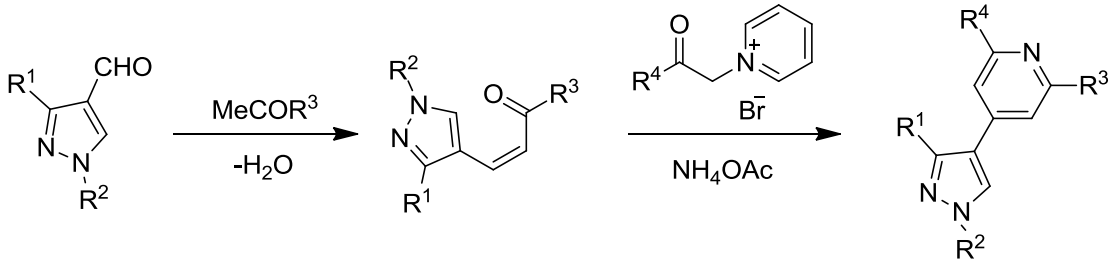
Condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with 2-cynomethyl-4-thiazolinone in ethanol containing a few drops of piperidine yielded methylene derivative [El-Emary et al 2005].



Lebedev et al (2005) reported the formation of 3-substituted pyrazole-4-carbaldehyde on treatment of several semicarbazones, derived from alkyl, phenyl, and cycloalkyl methyl ketones, with Vilsmeier Hacck reagent.

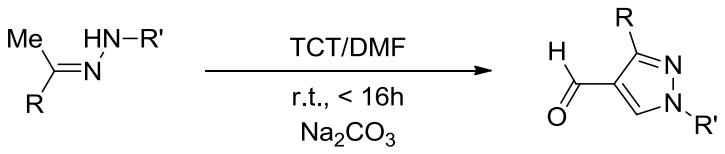


The reaction of 1,3-diaryl-1*H*-pyrazole-4-carbaldehydes with various substituted acetophenones in methanol in the presence of sodium ethoxide gave the corresponding α,β-unsaturated ketones which on refluxing with different phenacyl pyridinium bromides in acetic acid in the presence of ammonium acetate under Krohnke's conditions gave pyridinylpyrazoles in good yields [Reddy et al 2005].



Lidia et al (2004) reported the synthesis of 3-aryl(alkyl)-1-phenyl-1*H*-pyrazole-4-

carbaldehydes from the corresponding methyl ketone hydrazones by treating with cyanuric chloride in DMF at room temperature.



5. Technical programme

i) Name of the experiment: Synthesis, Characterization and biological evaluation of 4-functional pyrazoles and their derivatives.

ii) Location of study: Chemistry Lab at Eternal University.

iii) Methodology:

a) Source of literature

Chemical abstracts, Indian Journal of Chemistry, Arkivoc, Indian Journal of Heterocyclic Chemistry, Asian Journal of Chemistry, Indian Journal of Pharmaceutical Sciences, Tetrahedron Letters, Tetrahedron, Journal of Indian Chemical Society, Iranian Journal of Pharmaceutical Research, Journal of Brazilian Chemical Society, and European Journal of Medicinal Chemistry etc.

b) Pre-laboratory work

The chemicals & reagents required for the synthesis of proposed compounds will be procured from reputed chemical suppliers like Merck, Ranbaxy, Qualigens, Himedia etc.

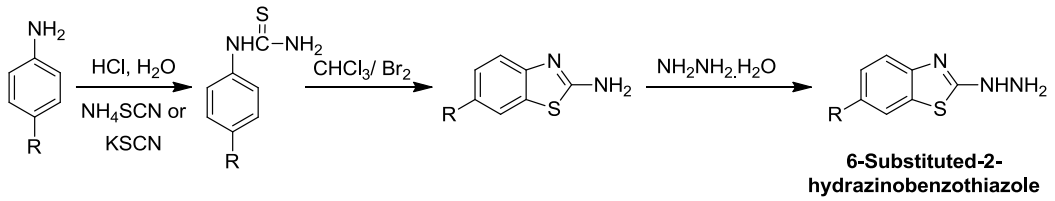
c) Laboratory work

Step 1: Synthesis

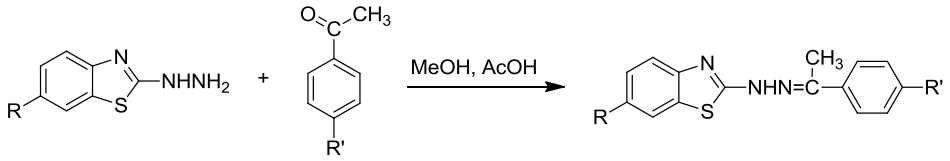
It will include standardising the reaction conditions for the synthesis of target compounds. Conventional methods of synthesis will be attempted. The completion of the reaction will be monitored by TLC. Advantages and feasibility of the methods will be analysed.

Plan of Work:

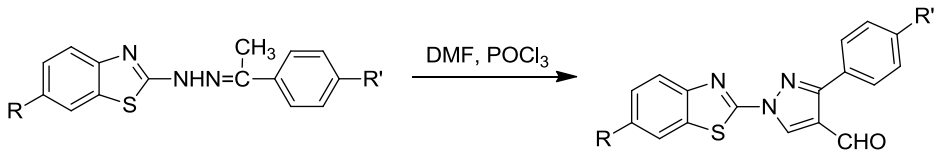
i. Synthesis of 2-hydrazino-6-substituted benzothiazoles



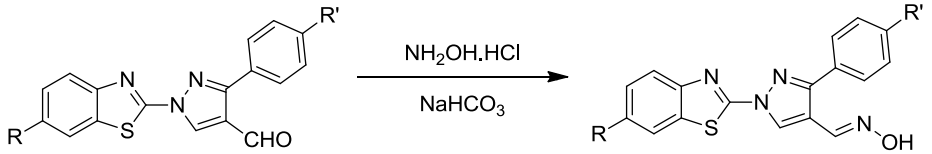
ii. Synthesis of 1-(4-substituted phenyl)ethanone (6-substituted benzothiazol-2-yl)hydrazones



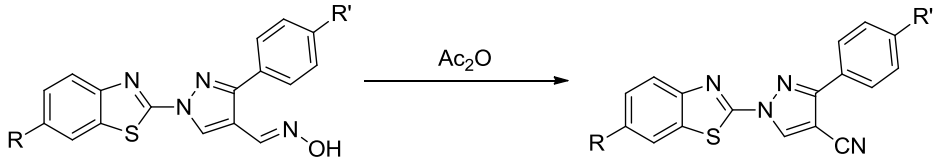
iii. Synthesis of 4-formylpyrazoles



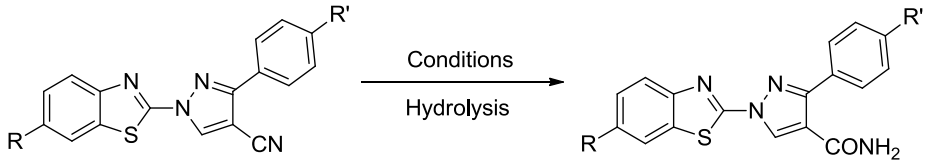
iv. Synthesis of 1*H*-pyrazole-4-carbaldehyde oximes



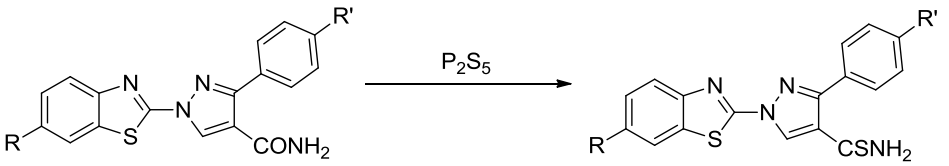
v. Synthesis of 4-cyanopyrazoles



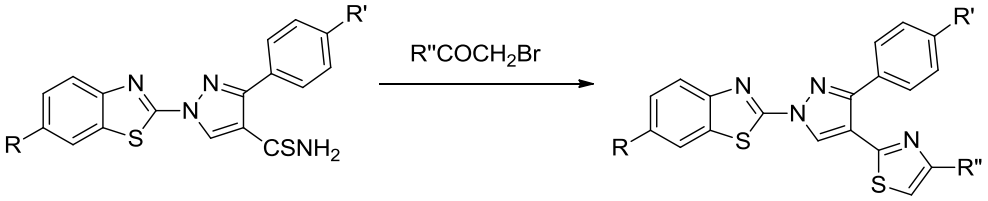
vi. Synthesis of 1*H*-pyrazole-4-carboxamides



vii. Synthesis of 1*H*-pyrazole-4-carbothioamides



viii. Synthesis of 1*H*-pyrazolylthiazoles



Step 2: Purification

The synthesized compounds will be purified by different methods like fractional distillation, recrystallization, and column chromatographic methods. The purity will be ascertained by TLC.

Step 3: Characterization

The synthesized compounds will be characterized by:

- Chemical tests for important functional groups.
- With various spectroscopic methods like IR, NMR, MS/LCMS etc.

iv) Observation to be recorded

- State of the compound (solid/liquid)
- If solid, colour of the compound
- Melting point if the compound is solid
- Yield of each compound
- Record and Interpretation of IR, NMR, MS and other spectra as per requirements to characterize the desired compound.

6. References

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